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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,475	12/30/2003	Masad J. Damha	MGU-0025	7556

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

SUPPLEMENTAL **Office Action Summary**	**Application No.** 10/748,475	**Applicant(s)** DAMHA ET AL.	
	Examiner Kimberly Chong	**Art Unit** 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

SUPPLEMENTAL DETAILED ACTION

This supplemental action contains a corrected PTO Form 326.

Status of Application/Amendment/Claims

Applicant's response filed 01/18/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 09/21/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 01/18/2007, new claims 11-18 are pending in the application. Applicant has canceled claims 1-10.

The rejections of record filed 09/21/2006 of claims 1 and 3-8 are rejected under 35 U.S.C. 112, first paragraph and under 35 U.S.C. 103(a) are obviated due to cancellation of said claims in the response filed 01/18/2007.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "...a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

The claims are drawn to a broad genus of compositions comprising an inhibitory agent comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1and wherein the inhibitory agent binds to the RNase H domain of retroid reverse transcriptase thereby inhibiting RNase H activity.

The instant claims and specification fail to provide adequate written description of the genera of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that is commensurate in scope with the breadth of the instant invention: binding of the inhibitory agent to any RNase H domain of retroid reverse transcriptase thereby inhibiting any RNase H activity.

The specification, in Example 8, discloses an embodiment wherein HIV-1 reverse transcriptase RNase H is inhibited using RNA dumbbells. The specification, in Example 11, discloses a specific embodiment wherein RNA dumbbells were used to inhibit either *E. coli* or Human RNase H activities. The specification, in Example 12, discloses a specific embodiment wherein RNA dumbbells and RNase H are crosslinked.

The specification does not provide a core structure sequence of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that would bind to bind to any RNase H domain of retroid reverse transcriptase and inhibit the activity of any RNase H. Therefore in only disclosing minimal examples of RNA dumbbells that inhibit RNase H activity in an assay, the specification does not provide adequate written description for the genus of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ

ID NO: 1 that provide the asserted function of binding to any RNAse H domain and inhibition RNase H activity.

The specification as filed does not provide specific guidance that would lead one of skill in the art to the claimed invention. Furthermore, the state of the art cannot provide the specific guidance as evidenced by Joshi et al. (Journal of Virology 2002). Joshi et al. teach identification of aptamer inhibitory agents targeted to the reverse transcriptase of HIV-1 is accomplished by screening a library of randomized sequences to find an inhibitory agent capable of binding to the reverse transcriptase region with high affinity. Joshi et al. further teach the sequences identified as binding with high affinity lack primary sequence homology to each other (see page 6545). Because the prior art teach identification of aptamer inhibitory agents that bind with high affinity to the reverse transcriptase region of HIV-1 must be done by screening a library of randomized sequences and teach each of the identified sequences lack homology with each other, one of skill in the art would not know which sequence, from a broad genus of inhibitory agents claimed, would provide the instantly claimed function of binding to any reverse transcriptase and inhibiting the function of any RNase H.

Moreover, MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the

operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).

Therefore, in the instant application, Applicants have not shown possession of the entire claimed genus of inhibitory agents comprising two antiparallel complementary regions wherein said regions are 2', 5'-linked or 3', 5-linked ribonucleotides and further comprising at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1 that would bind to the RNase H domain and inhibit RNase H activity.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

The foregoing represents a new rejection, however Applicant's arguments will be addressed since the applicant's arguments filed 01/18/2007 would apply to the new claims.

Applicants have traversed the 112 second rejection and argue a core structure of inhibitory agents has in fact been provided and have provided multiple species of the clamed genus that demonstrates applicants were in possession of the instantly claimed invention. Applicants further argue the teachings of Joshi et al. are not relevant to the clamed agents that bind to the RNAse H domain of a retroid virus because Joshi et al. teach agents that block the reverse transcriptase function. Applicant's arguments are not found persuasive.

The teachings of Joshi et al. was relied upon to point out that that it is recognized in the art that identifying an aptamer targeted to a protein, HIV reverse transcriptase for example, is accomplished by screening a large library of randomized sequences because such sequences that bind with high affinity lack primary sequence homology to each other. The teachings of Joshi et al. coupled with the lack of adequate written description in the specification for the broad genus of inhibitor agents with the asserted function of binding to any RNAse H domain and inhibiting RNAse H activity would not allow one skilled in the art to reasonably conclude that the inventor had possession of the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wasner et al. (cited Form PTO-1449 filed 10/04/2004) in view of Hannoush et al. (cited Form PTO-1449 filed 10/04/2004) of Ray et al. (cited on PTO Form 892 filed 01/11/2006) and Clusel et al. (cited on PTO Form 1449 filed 10/04/2004).

The instant claims are drawn to a composition comprising an inhibitory agent comprising two complementary regions linked by 2', 5' ribonucleotides at least 4 nucleotides in length comprising the sequence provided as SEQ ID NO: 1, wherein the

complementary regions are between 2 and 24 nucleotides in length and comprise an arabinonucleic acid, 2'-fluoro-arabinonucleic acid, locked nucleic acid, peptide nucleic acid or a combination thereof and the complementary region is comprised of deoxyribonucleic acid or ribonucleic acid, wherein the loop regions comprise from 2 to 8 nucleotides in length, wherein the complementary regions are comprised of 3-, 5'-linked ribonucleic acid, deoxyribonucleic acid or a combination of both, wherein the complementary region comprises a 3-, 5'-linked ribonucleic acid that are 4 to 10 nucleotides in length, the by 2', 5' linked ribonucleotides are a 3', 5'-linked tetranucleotide (SEQ ID NO:1) and wherein the composition is a cyclic structure.

Wasner et al. teach a nucleic acid compound for inhibiting the RNAse H activity of a retroid virus reverse transcriptase comprising two complementary strands 18-23 nucleotides in length, wherein the strands can be RNA or DNA or both and further wherein the duplex comprise 3', 5'-linked or 2', 5'-linked RNA (see Figure 1 and Table 1). Wasner et al. recognized that although the nucleic acid duplexes were capable of inhibiting RNase H activity, they had low thermal stability properties (see page 7482 and Table 2). Moreover, Wasner et al. specifically teach along with the utility of said nucleic acid molecules and their analogues in antiretroviral applications, "...hairpin 'aptamers' designed with the proper combination 2', 5 RNA and (complementary) RNA segments may inhibit the removal of the RNA component of the RNA:DNA hybrid formed during reverse transcription."

Hannoush et al. teach hairpin structures comprising tetranucleotide loops are extremely stable and are important structural motifs for the design of nucleic acid aptamers.

Clusel et al. teach double stranded dumbbell oligonucleotides have increased stability because of the incorporation of hairpin loops at the ends of the duplex structures (see Table 1).

Ray et al. teach peptide nucleic acids are synthetic molecules that can bind with high sequence specificity to a chosen target in a gene sequence and further Ray et al. teach that hybrid nucleic acid complexes containing a peptide nucleic acid exhibit extreme thermal stability and unique ionic strength. Therefore, one of skill in the art would have been motivated to incorporate PNAs to increase duplex stability in a duplex nucleic acid.

It would have been obvious to one of skill in the art to incorporate hairpin loops at both ends of an aptamer, as taught by Clusel et al. It would have been further obvious to one of skill in the art to incorporate specifically tetranucleotide loops as taught by Hannoush et al. and to incorporate PNAs to further increase the duplex stability as taught by Ray et al.

One of skill in the art would have clearly been motivated to incorporate hairpin structures into the inhibitory agent taught by Wasner et al. for the use in inhibition RNase H activity because Clusel et al. teach that oligonucleotides provide a potential therapeutic tool to control expression of specific genes involved in viral diseases and one of the major obstacles to be solved in to reduce the sensitivity to nucleases. Clusel

et al. teach that dumbbell oligonucleotides have increased nuclease resistance and these oligonucleotides still have efficient binding affinity for the desired protein (see page 3410). Because Hannoush et al. teach tetranucleotide loops identical to the instantly clamed SEQ ID No. 1 are extremely stable and are important structural motifs for the design of nucleic acid aptamers, one of skill in the art would have been motivated to incorporate the tetranucleotide loops on both ends to create a dumbbell oligonucleotide. The motivation to incorporate PNAs is given by Ray et al. who. teach peptide nucleic acids are synthetic molecules that can bind with high sequence specificity to a chosen target in a gene sequence and further Ray et al. teach that hybrid nucleic acid complexes containing a peptide nucleic acid exhibit extreme thermal stability and unique ionic strength. Therefore, one of skill in the art would have been motivated to incorporate PNAs to increase duplex stability in a duplex nucleic acid.

The teaching of Wasner et al., Clusel et al., Hannoush et al. and Ray et al. provide a reasonable expectation of success given that Wasner et al. and Hannoush et al. teach inhibition of RNAse activity using said duplex and because Ray et al. teach targeting a gene sequence using a duplex comprising a peptide nucleic acid and further teach inhibition of gene activity using a duplex comprising a peptide nucleic acid. Additionally, one would have a reasonable expectation of success given that Hannoush et al. teach that an oligonucleotide duplex comprising a tetranucleotide loop having the sequence identical to SEQ ID NO. 1 increase the duplex thermostability and further teach the actual hybrid duplex taught in Wasner et al., which was shown to inhibit RNase H activity, is more stable when linked to the said tetranucleotide loop.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The foregoing represents a new rejection necessitated by the cancellation of the claims and the filing of new claims, however applicant's arguments with regard to the references will be addressed briefly since they would apply to the new rejection.

Applicants sole argument is that statements made in the prior rejection of record filed 09/21/2006 state that because the prior art, such as Ray et al., teach targeting gene sequences and inhibiting gene activity, there is no basis for combining the cited references in order to produce a ligand which binds to the RNase H domain of a retroid virus reverse transcriptase. Applicant's arguments are not convincing.

Wasner et al. specifically sate utility of said nucleic acid molecules taught and their analogues are useful as hairpin aptamers i.e. ligands, in antiretroviral applications. Hannoush et al. teach tetranucleotide loops are important structural motifs for the design of nucleic acid aptamers i.e. ligands. Further, although Ray et al. does not specifically teach incorporate of PNAs in aptamers, Ray et al. teach the usefulness of PNAs to increase the stability of nucleic acids and one of skill in the art would have been motivated and have had a reasonable expectation of success at incorporating PNAs into nucleic acids that are used in therapeutic applications. As such, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kimberly Chong
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